PARTICIPANT INFORMATION SHEET
CLINICAL TRIAL

The effect of nutraceutical supplement (Thompson's Super Bioflavonoid Complex®) on blood glucose levels in prediabetes and type 2 diabetes – A Pilot Study.

Invitation

You are invited to participate in a research study to assess the effect of using the nutraceutical supplement "Thompson's Super Bioflavonoid Complex®", which contains citrus bioflavonoid extract-500 mg, ascorbic acid-390 mg, rutin-100 mg, and sodium ascorbate-125.3 mg (equiv 110 mg Ascorbic Acid) on blood glucose levels in prediabetes and type 2 diabetes.

Type 2 diabetes is a chronic disease where the body doesn't produce enough insulin hormone to reduce blood glucose levels or the body resists the action of insulin. This disease is characterised by an increased thirst, frequent urination, hunger, fatigue and blurred vision.

The study is being conducted by:

- Dr. Kiran Ahuja, Dr. Glenn Jacobson, Dr. John Burgess, Dr. Hayder Al-Aubaidy, and Mr. Ankit Gupta, Diabetes Research Group, Medical Science Precinct/School of Health Sciences, University of Tasmania (UTAS).

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. 'What is the purpose of this study?'

This study aims to determine the significance of nutraceutical supplement which is Thompson's Super Bioflavonoid Complex®) on blood glucose levels in patients with type 2 diabetes.

2. 'Why have I been invited to participate in this study?'

You have been invited to participate in this study because you:

i) Have clinically diagnosed with prediabetes/type 2 diabetes.
ii) Aged between 25 – 75 years.
iii) Have normal or controlled blood pressure.
iv) Willing to take nutraceutical supplements (Thompson's Super Bioflavonoid Complex®) for 12 weeks.
v) Not Pregnant

3. 'What if I don't want to take part in this study, or if I want to withdraw later?'
Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

New information about the treatment being studied may become available during the course of the study. You will be kept informed of any significant new findings that may affect your willingness to continue in the study. If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason. Any clinical data or samples taken prior to withdrawal will still be used in our analysis anonymously (i.e. your name or identifiable information will not be linked to the clinical outcome).

4. 'What does this study involve?'

Participants will be randomly allocated into two groups -Study Group and Control Group (25 participants in each group): Study group (Group-1) include participants who use the Thompson's Super Bioflavonoid Complex® for 12 weeks and continue on their current anti-diabetic treatment with no interruption. Control group (Group-2) include participants who use the placebo tablets for 12 weeks and continue on their current anti-diabetic treatment with no interruption.

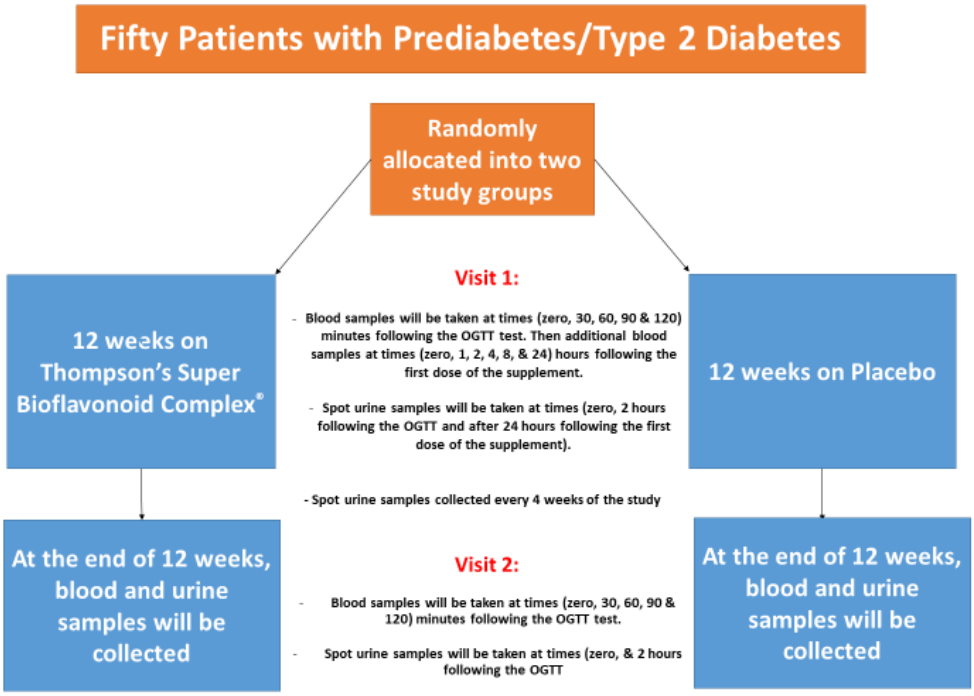

Figure 1: Overview of the study.

Participants:

Inclusion Criteria-:
For all participants

1. Have been clinically diagnosed with prediabetes and/or early stage type 2 diabetes (on diet and lifestyle intervention or metformin only treatment).
2. Aged between 25 – 75 years.
3. Lean, overweight or obese (BMI 19-35 kg/m^2).
4. Have normal or controlled blood pressure (Seated brachial blood pressure <140/90 mmHg).
5. Have given signed informed consent to participate in the study.
6. Willing to take nutraceutical supplement (Thompson's Super Bioflavonoid Complex®), for 12 weeks.

Exclusion Criteria-:
For all participants

1. Age <25 yrs or >75 yrs
2. Morbidly obese with a BMI ≥35 kg/m2
3. Not on diet and lifestyle or metformin only treatment for their diabetes (e.g. insulin injections, sulphonylureas, GLP-1 receptor agonists), or clinically diagnosed with type 1 diabetes.
4. History of myocardial infarction or stroke
5. History of malignancy within past 5 years (except for non-melanoma skin cancers)
6. Identification of any medical condition requiring immediate therapeutic intervention
7. Uncontrolled hypertension (resting brachial blood pressure ≥160/100 mmHg)
8. History of severe liver disease
9. History of drug or alcohol abuse
10. Elective major surgery during the course of the study
11. Pregnancy/lactation
12. Currently consuming nutraceutical supplements (especially vitamin C and D)
13. Participation or intention to participate in another clinical research study during the study period.
14. Not willing to take nutraceutical supplements (Thompson's Super Bioflavonoid Complex®), for 12 weeks.
15. Participants with impaired renal function.

VISIT 1

If you agree to participate in this trial, you will be asked to fast overnight (i.e. not eat food and only drink water on the morning of the study) and stop taking metformin and

then undergo the following procedures at the Medical Science Precinct/School of Health Sciences, UTAS:

- A medical/health questionnaire to confirm eligibility.
- A physical activity questionnaire, completing a food diary form
- Your height, body weight and waist circumference measured.
- Your blood pressure measured.
- Blood samples will be collected using phlebotomy and cannulation.
- An oral glucose tolerance test to measure your glucose tolerance and insulin sensitivity. This requires drinking 25g of glucose (sugar drink) and a sample of blood taken from your vein before and at 0, 30, 60, 90 and 120 minutes after drinking the glucose solution (Make sure to come fasting on the day of appointment). You will be asked to wait in the clinic area for an additional time. Blood glucose will be measured every 30 minutes. You will be discharged when your blood glucose level return to normal range.
- Your blood pressure and vascular health will be measured using a blood pressure cuff placed on your upper arm.
- Urine sample to measure kidney function, electrolytes and oxidative stress.
- Pregnancy test for woman during their reproductive life
- Pharmacokinetics/pharmacodynamic study:

  During visit 1, and after the first dose of Thompson's Super Bioflavonoid Complex® supplementation/ Placebo, additional blood and urine samples will be collected following the first dose of the supplement to measure the activity of a single dose administration of the citrus bioflavonoid in human body. A series of blood and urine samples will be collected at times (0, 1, 2, 4, 8 and 24) hours following the initial dose of the supplement. During the first 4 hours, participants will be able to move around but need to stay within the clinical area, light snacks and fruits will be provided. After the first 4 hours, participants can leave and come back for the 8 hrs and 24 hrs time of collection.
- Participants on metformin will be able to take their next dose of the medication after they drink the oral glucose load.

SUPPLEMENTATION PHASE

Thompson's Super Bioflavonoid Complex® supplementation/ Placebo:

You will be randomly divided in either of the two groups. If you get allocated to the study group (Group-1), you will be asked to take 2 tablets of Thompson's Super Bioflavonoid Complex® daily before/with the meal (either lunch or breakfast) for 12 weeks (total of 168 tablets per participants). If you get allocated to the control group (Group-2), you will be asked to take placebo tablets daily before/with the meal (either lunch or breakfast) for the whole 12 weeks. The Thompson's Super Bioflavonoid Complex®/Placebo tablets will be provided free of charge, for the entire length of the study. However, if you skip 42 tablets (equivalent to 3 weeks) over the course of the study, you will be excluded from the study.

You will be asked to complete a logbook to record the day and time you take the tablets as well as not to change any other lifestyle factors (e.g. diet or level of physical activity). During the last week of the Thompson's Super Bioflavonoid Complex® supplementation/Placebo study, you will be asked to repeat the food questionnaire and the physical activity questionnaire. This can be filled out at home and brought to the clinic on visit 2.

You should consult with your general practitioner prior to the participation in this study including either placebo or Thompson's Super Bioflavonoid Complex®, because you may need to modify your medication for diabetes.

VISIT 2 - WEEK 12 TESTING:
Following the 12 weeks of Thompson's Super Bioflavonoid Complex® /Placebo, you will be asked to fast overnight (i.e. not eat food and only drink water on the morning of the study) and stop taking metformin and then undergo the following procedures at the Medical Science Precinct/School of Health Sciences, UTAS:

- Finger Prick method for testing blood glucose level using glucometer
- An oral glucose tolerance test to measure your glucose tolerance and insulin sensitivity. This requires drinking 25g of glucose (sugar drink) and a sample of blood taken from your vein before and at 0, 30, 60 90 and 120 min after drinking the glucose solution. You will be asked to wait in the clinic area for an additional time. Blood glucose will be measured every 30 minutes. You will be discharged when your blood glucose level return to normal range.
- Your blood pressure and vascular health will be measured using a blood pressure cuff placed on your upper arm.
- Urine sample to measure kidney function, electrolytes and oxidative stress.
- Body composition measurement (height, weight, waist and hip circumference).
- Participants on metformin will be able to take their next dose of the medication after they drink the oral glucose load

5. 'How is this study being paid for?'
The study is funded by Tasmanian Community Fund and University of Tasmania.

6. 'Are there risks to me in taking part in this study?'
All medical procedures involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions, you might develop medical complications from participating in this study. Other known risks of this study which may be related to performing the oral glucose tolerance test include:

- Discomfort associated with having blood samples taken including bruising.

- Slight increase in blood glucose levels due to the intake of oral glucose load. Since we are using a low glucose load (25 gm), this will not cause a significant rise in the blood glucose levels.
- Side effects associated with Thompson's Super Bioflavonoid Complex® tablets.
  i) Allergy.
  Mild Hypoglycaemia.

You should consult with your general practitioner prior to the participation in this study including either placebo or Thompson's Super Bioflavonoid Complex®, because you may need to modify your medication for diabetes.

7. 'What happens if I suffer injury or complications as a result of the study?'

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies. You do not give up any legal rights to compensation by participating in this study.

If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

8. 'Will I benefit from the study?'

This study aims to assess the effect of using nutraceutical supplements as anti-diabetic medications (DPP-4 inhibitors) in people with prediabetes and type 2 diabetes.

9. 'Will taking part in this study cost me anything, and will I be paid?

Participation in this study will not cost you anything. In addition, you may be reimbursed for parking during your clinic visits to the Medical Science Precinct/School of Health Sciences, UTAS as well as free food (nibbles and snacks) after the completion of blood sampling.

10.'What will happen to my blood/urine sample after it has been used?'

The blood and urine samples you provide during the study will be stored in a freezer and tested for biochemical markers related to insulin resistance, diabetes and cardiovascular

disease (e.g. metabolites, lipids, inflammatory markers, insulin). The samples will be destroyed 15 years after completion of the study. If you do agree to your samples being stored, they will not be used for other research projects, except with your written consent or, under some circumstances, with the approval of a Human Research Ethics Committee at that time.

11. 'How will my confidentiality be protected?'

The investigators, doctors and staff involved in the study will know whether or not you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Only the researchers named above will have access to your details and results that will be held securely at the Medical Science Precinct/School of Health Sciences, UTAS.

12. 'What happens with the results?'

If you give us your permission by signing the consent document, we plan to publish the results in peer-reviewed journals and present the findings at scientific conferences. In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish.

13. 'What happens to my treatment when the study is finished?'

The study will be stopped after its completion. You will need to bring all the unused supplements when you come to your next appointment. If you missed a total of 3 weeks' supplements, then you will not be included in this study. We recommend you consult with your treating doctor if you decide to continue the intake of Thompson's Super Bioflavonoid Complex® tablets.

14. 'What should I do if I want to discuss this study further before I decide?'

When you have read this information, the researcher will discuss it with you and any queries you may have. If you would like to know more at any stage, please do not hesitate to contact Dr. Kiran Ahuja/ Dr. Glenn Jacobson on 03 6324 5478/ 03 6226 2202.

15. 'Who should I contact if I have concerns about the conduct of this study?'

This study needs to be approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study you should contact the Executive Officer of the HREC (Tasmania) Network on (03) 6226 7479 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. You will need to quote [*HREC project number H15762*].

Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.
This information sheet is for you to keep.